THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Protocol Abstract Page

Study Chairman:	Charles Lu, MD, SM
Department:	Thoracic/Head & Neck Medical Oncology
Phone:	713-792-6363
Box:	80
Study Co-Chairman:	Jack A. Roth, MD Thoracic and Cardiovascular Surgery

Full Title: Phase I Study Of Intravenous DOTAP:Cholesterol-Fus1 Liposome Complex (DOTAP:Chol-*fus1*) In Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Previously Treated With Chemotherapy

Objectives:
Assess the toxicity of DOTAP:Cholesterol-fus1 Liposome Complex (DOTAP:Chol-fus1) administered intravenously.
To determine the maximal tolerated dose and recommended phase II dose of DOTAP:Chol-*fus1* administered intravenously.
Assess the expression of *fus1* following intravenous delivery of DOTAP:Chol-*fus1* in tumor and normal bronchial epithelial cell biopsies.
Assess any anti-cancer activity for DOTAP:Chol-*fus1*.

Rationale: (Be concise as possible)

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the United States. Patients with recurrent or locally advanced, unresectable stage IIIB (pleural effusion) or stage IV NSCLC are currently treated with palliative chemotherapy-based treatments. With the most active chemotherapeutic agents, median survival has been demonstrated to increase by several months. Clearly new therapeutic agents are needed.
The results from the preclinical studies of intravenous delivery of tumor suppressor genes complexed to DOTAP:Chol show reduction of experimental metastases and prolongation of survival in a SCID mouse human lung cancer model and justify a clinical trial to assess toxicity as a prelude to possible efficacy studies. The *fus1* gene has been selected because of its high degree of selective apoptosis for lung cancer cells compared to normal bronchial epithelial cells, its ability to completely inhibit the growth of subcutaneous tumors with intratumoral injection, and its ability to mediate a reduction in lung experimental metastases of >80% which is comparable to p53. It is likely that this gene will be deleted in the early stages of lung carcinogenesis thus making it an attractive target for all stages of disease. Extensive toxicity studies have been conducted in mice and show that intravenous doses of the DOTAP:Chol-*fus1* complex up to 100 μg are tolerated without toxicity. Mice have received up to six consecutive daily doses of 50 μg without toxicity.

Eligibility Criteria: (List Major Criteria)

Inclusion:
Histologically or cytologically documented non-small cell lung cancer (NSCLC). Recurrent or locally advanced, unresectable stage IIIB (pleural effusion) or stage IV NSCLC. Patients must have received at least one prior chemotherapy regimen for recurrent or locally advanced, unresectable stage IIIB (pleural effusion) or stage IV NSCLC. There is no limit to the number of prior chemotherapy regimens received. Preference will be given to patients with excellent performance status and tumors amenable to biopsy. Patients must have a life expectancy of at least 12 weeks. Karnofsky Performance Status ≥ 70%. Negative serum pregnancy test (serum HCG) if female and of childbearing potential (non-childbearing is defined as greater than one year post-menopausal or surgically sterilized). Negative serology for Human Immunodeficiency Virus. Patients have recovered from any surgical procedure. ANC > 1500 x $10^9/mm^3$, plt count > 100,000 x $10^9/mm^3$. PT < 14 sec, PTT < 38 sec. Adequate renal function documented by serum creatinine of ≤ 1.5 mg/dl or calculated creatinine clearance > 50 ml/min. Adequate hepatic function as documented by serum bilirubin< 1.5 mg/dl and SGOT (ALT). Stable cardiac condition (New York Heart Classification <III). FEV1 of >30% of predicted.

Exclusion:
Pregnant or lactating females. Patients who received chemotherapy within 30 days of entry into the protocol. Active systemic viral, bacterial or fungal infections requiring treatment. Patients with brain metastases. Patients with serious concurrent illness or psychological, familial, sociological, geographical, or other concomitant conditions that do not permit adequate follow-up and compliance with the study protocol. Use of any investigational agent within four weeks of study treatment. Prior gene therapy.

Treatment Plan:

The LD_{10} for a single intravenous dose in the mouse is 100μg and thus a starting dose for patients of 0.02mg/Kg given intravenously was selected based on extrapolations from the mouse surface area to humans (1/20 LD_{10}). This clinical trial will be a dose escalation trial. The trial design will be based on a continuous reassessment model (CRM) which allows the maximum tolerated dose to be periodically re-estimated (see Section 10). Patients entered at a given dose level will not be eligible for dose escalation while on study. A cohort of 3 patients will be treated at each dose level. After treating 3 patients at a given dose level, the patients will be observed for 2 weeks to evaluate the toxicity. The information of whether the patients develop dose limiting toxicity (DLT) will be recorded for computing the posterior probability of toxicity given the prior and the data. The next cohort of patients will be treated at the dose level having the posterior probability of DLT closest to the pre-specified target toxicity level (TTL). All the patients will be treated in a dose-escalation fashion starting from the lowest level. The next dose level can be moved up if indicated by the calculation of the posterior distribution but no skipping of doses is allowed. A maximum of 30 patients will be treated in this Phase I trial.
Patients may receive up to six treatments at their specified dose level. The time interval between treatments is 3 weeks. Treatment will be stopped for any cumulative grade 3 (grade 4 hematologic) or greater toxicities or disease progression. Evaluation and measurement of primary and other disease sites with appropriate examination (clinical or radiological including CT scans) will be done every two treatment cycles (6 weeks). Patients will receive treatment as outpatients and will be monitored for two hours after each treatment.

Does your research involve the use of Recombinant DNA technology? **X Yes** No N/A –

If Yes, appropriate forms are obtainable through the Office of Research.

Statistical Considerations:
The primary objective for this Phase I study is to evaluate the toxicity of the Intravenous DOTAP:Chol-*fus1* complex and to determine the maximum tolerated dose (MTD) for the subsequent Phase II trials. We will apply the continual reassessment method (CRM) for this trial.

Patient Evaluation: (Pretreatment and Interim Testing)

Pretreatment Evaluation: Medical History, physical examination (weight, Zubrod performance status, vital signs), hematology (CBC with differential, platelets), prothrombin time, partial thromboplastin time, chemistry (calcium, sodium, potassium, chloride, phosphate, total protein, albumin, creatinine, alkaline phosphatase, SGOT, LDH, urea, and total bilirubin), serum HCG (if female of childbearing potential), HIV serology, urinalysis, pulse oximetry, baseline radiologic studies for tumor assessment, baseline EKG and MUGA scan.

Interim Testing: Prior to each additional treatment the following evaluation is required: Physical examination (weight, Zubrod performance status, vital signs), hematology (CBC with differential, platelets, chemistry (calcium, sodium, potassium, chloride, phosphate, total protein, albumin, creatinine, alkaline phosphatase, SGOT, LDH, urea, and total bilirubin), pulse oximetry. Restaging radiologic studies for tumor assessment will be performed after every two treatment cycles (every 6 weeks).

Optional biopsies of accessible tumor and normal bronchial mucosa for vector-specific RT-PCR and western blot assays will be performed prior to and 48 hours after the first treatment.

Estimated Accrual:

It is estimated that accrual will be 1-2 participants per month.